

PolyA Single Strand DNA Translocation through an α -Hemolysin pore stem

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Outline

Motivation: Rapid DNA sequencing
Voltage driven translocation in α -Hemolysin

A new model: PolyA, α -Hemolysin Interaction Energy

- Calculation: Polymer-Pore interaction energy $U(z)$.
- Polymer-pore interaction forces as a function of polymer length.

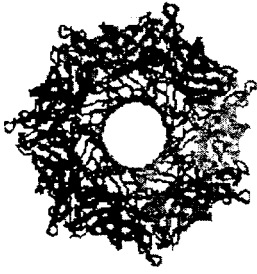
Polymer Translocation Simulation

- 1-D drift-diffusion : Smoluchowski equation.
- Translocation Velocity: Polymer length dependence
- Translocation time $T_{(L)}$: Pore geometry dependence.

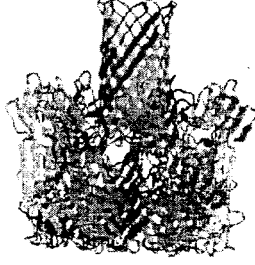
Conclusions

Motivation: Rapid DNA sequencing

α -hemolysin pore

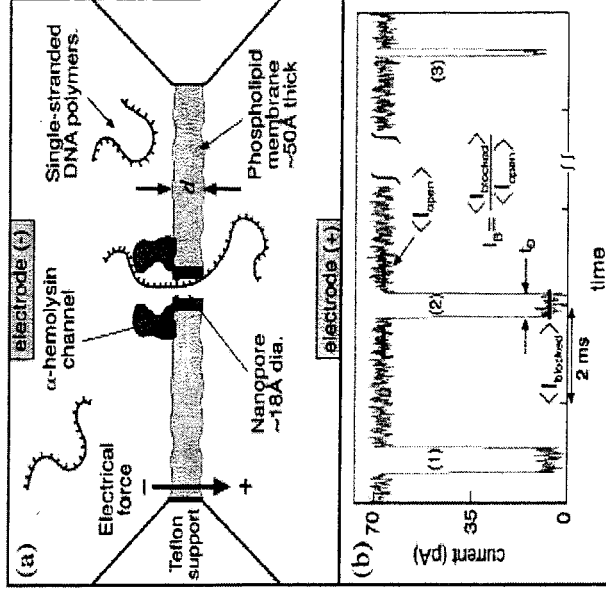
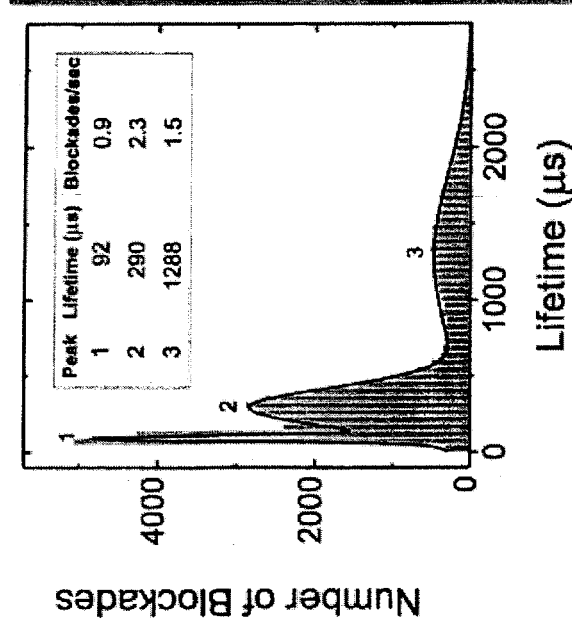


Axial View



Side View

*Branton et al. Harvard Nanopore group



- α -hemolysin pore can differentiate between single stranded homopolymers. (Akeson and Branton, J.Biophys. 77, 3227)
- Blockade current changes could be used to sequence DNA.

*Meller et al. PRL. 86 No.15

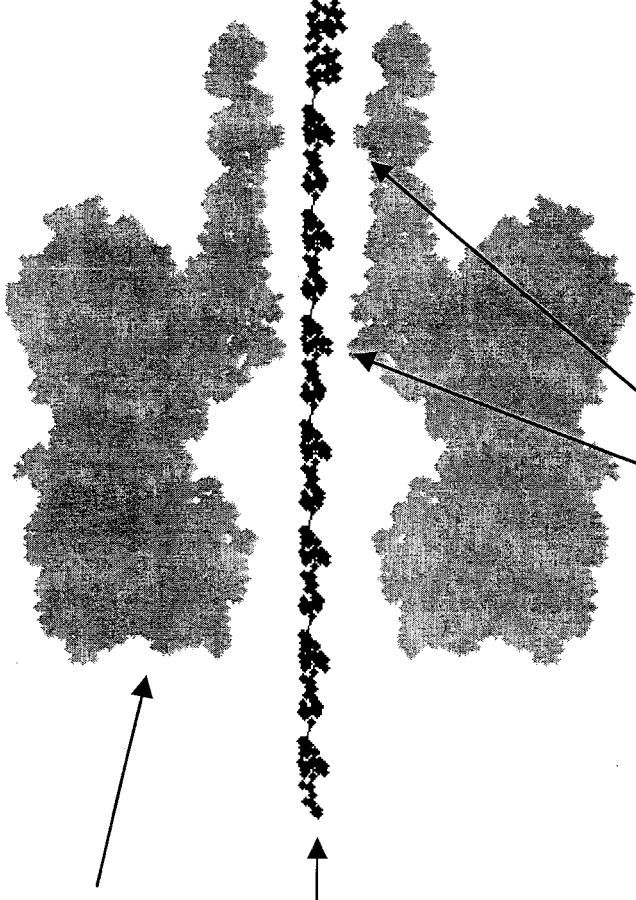
Motivation: Rapid DNA sequencing

The blockade current signature must be interpreted

Challenges:

α -hemolysin has 32305 atoms

~20 nucleotides can occupy the pore concurrently.



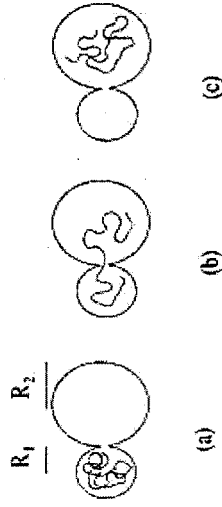
The small pore diameter results in strong coulombic and VanDer Waals interactions with the DNA



Simulation Approach

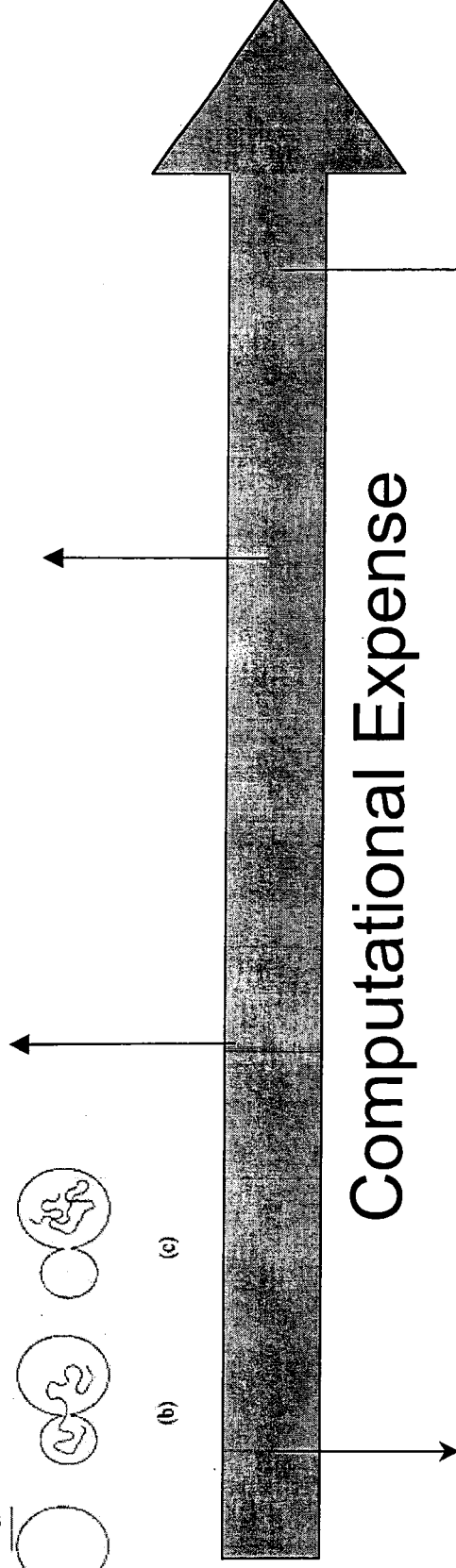
Gaussian Chain

- Calculates entropy barrier for polymer escape through a nanopore



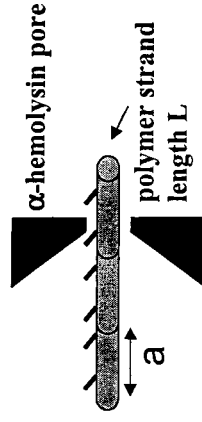
Hybrid Nerst-Plank (Our Approach)

- Atomistic calculation for interactions
- Polymer specific diffusion coefficients D_0
- Coarse-grain drift-diffusion dynamics



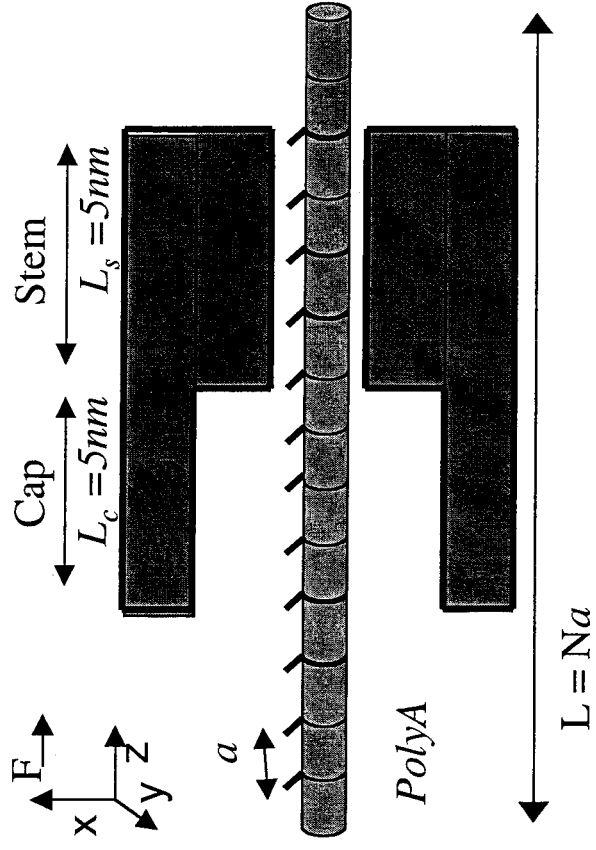
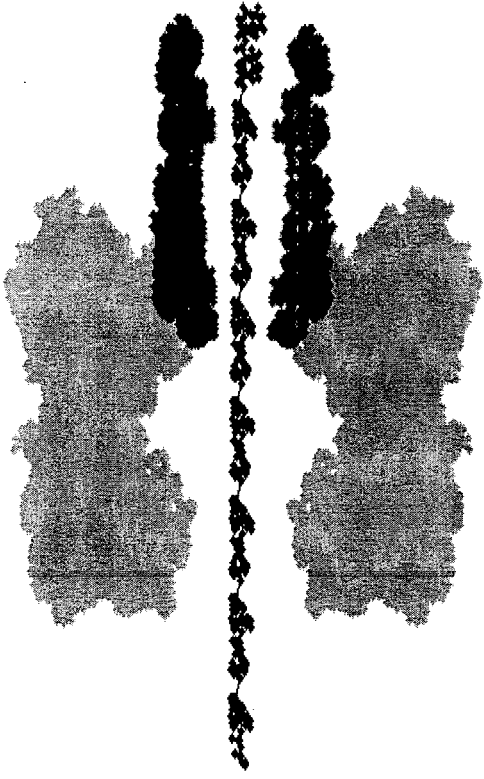
Drift-Diffusion

- Single point polymer-pore interaction
- Sawtooth polymer potential
- Infinite polymer length



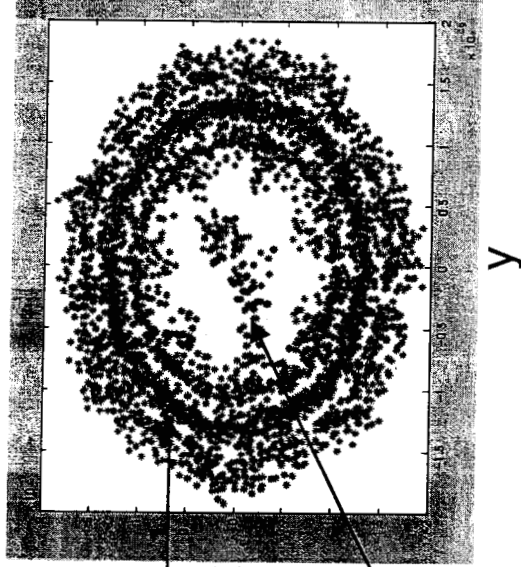
MD, computational chemistry

- ~30,000 pore atoms, 500 polymer atoms, ~1000 water molecules and ~100 ions.
- Pico second ion relaxation time
- Microsecond nucleotide translocation times



- The α -hemolysin pore is comprised of a wide Cap with diameter $\sim 4.2\text{nm}$ and a narrow Stem with a minimum diameter $\sim 1.2\text{nm}$.
- The strongest drag forces on the polymer occur in the stem.
- We consider the interaction of 3675 atoms in the stem with $N \cdot 32$ atoms in N nucleotides

Polymer-pore Interaction



Pore-stem Charge:
7 electrons

Polymer Charge:
N-1 electrons

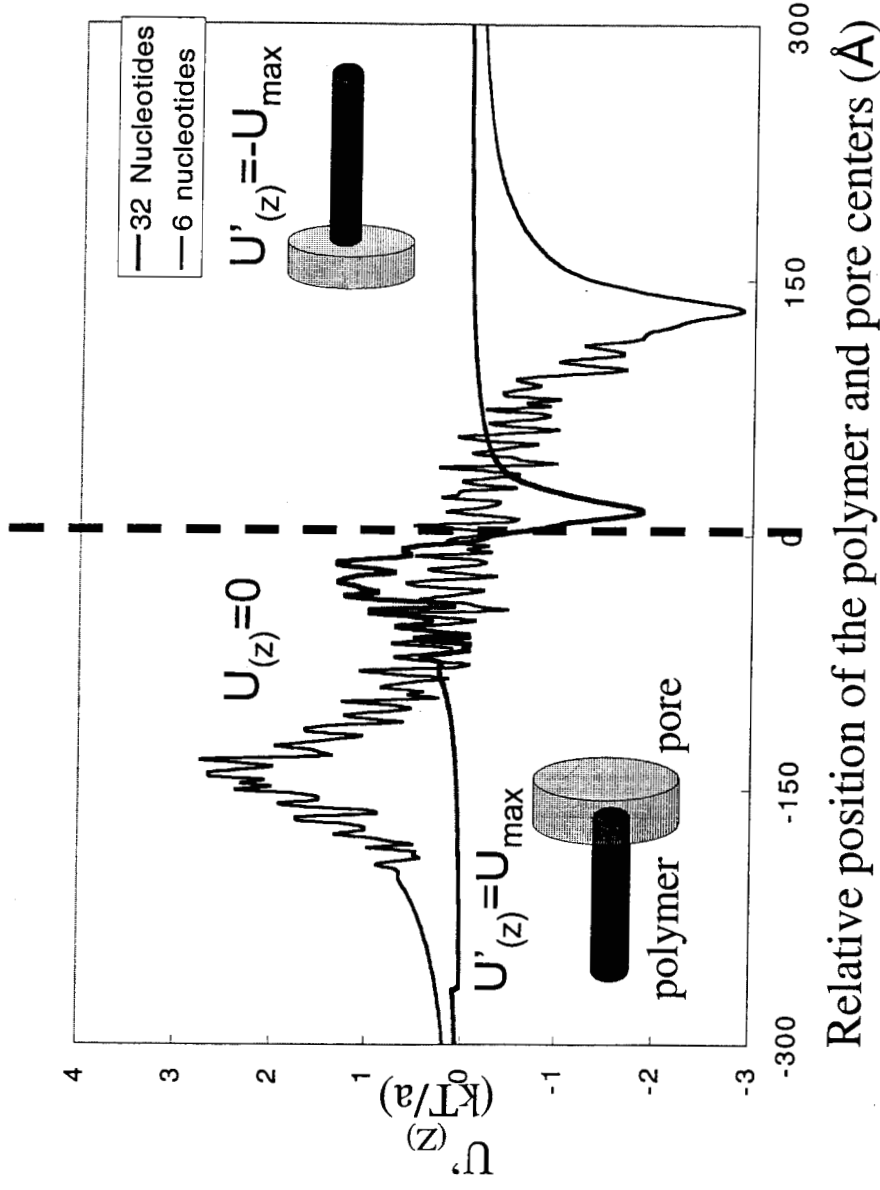
Polymer-Pore interaction potential U_T

$$U_T = U_{(ion - pore)} + U_{(ion - polymer)} + U_{(ionic - solution)}$$

Total Coulombic force on polymer $U = \sum_i \sum_j \frac{q_i q_j}{4\pi\epsilon(R_{ij})^2}$

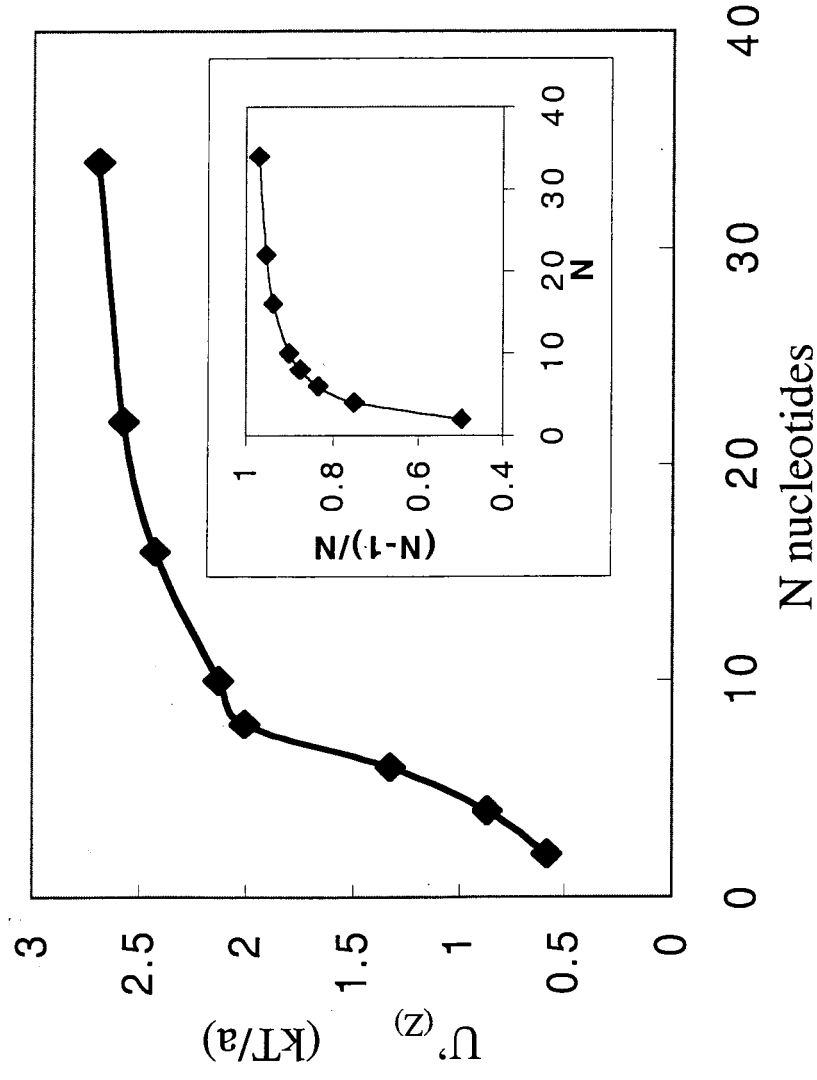
Force along polymer axes $U = \sum_i \sum_j \frac{q_i q_j}{4\pi\epsilon(R_{ij})^2} \frac{(z_i - z_j)}{|R_{ij}|}$

Interaction Potential as a function of polymer position



- The maximum of each curve represents the peak repulsion between the negatively charged polymer and pore.
- This energy barrier at the pore-stem entrance motivates the need for a voltage-driven translocation analysis.

Plot of peak repulsion as a function of polymer length



The peak polymer-pore repulsion is significantly reduced for $N < 10$ nucleotides. The insert shows how the average charge per nucleotide $(N-1)/N$ has a similar roll-off for short polymers ($N < 10$) as a result of the hydrogen terminations.

Polymer Translocation Simulation

1-D drift-diffusion: Smoluchowski equation

$P(z, t)$ The probability that a length z of the Polymer has passed through the pore in a time t .

$F(z)$ Driving electric field

$$\frac{\partial P}{\partial t} = D_0 \frac{\partial}{\partial z} \left[\frac{\partial P}{\partial z} + \frac{U'(z)}{k_B T} P \right]$$

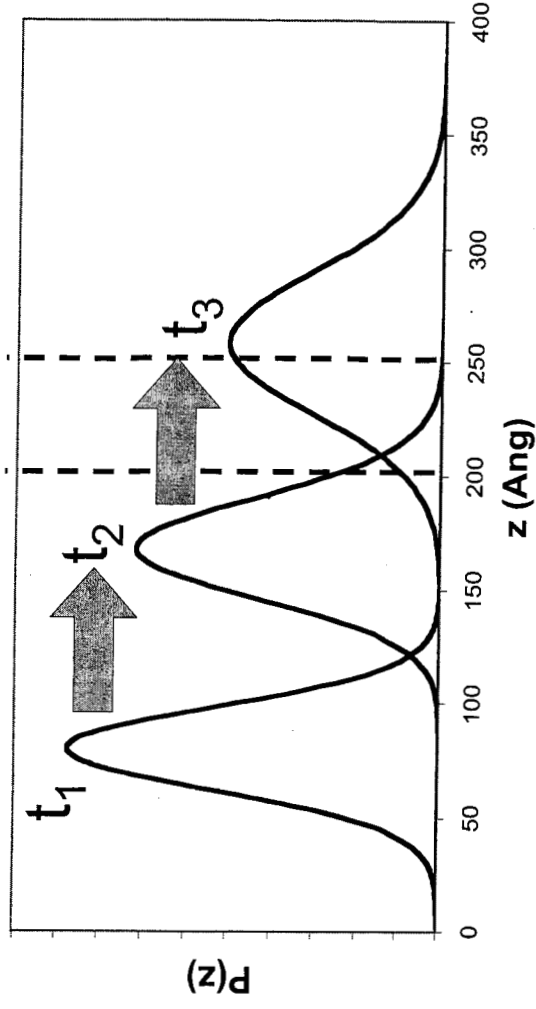
Diffusion

Drift under the influence of the polymer-pore interaction force $U'(z)$

Free space drift velocity

In the absence of any polymer-pore interaction the polymer has a drift velocity v_0

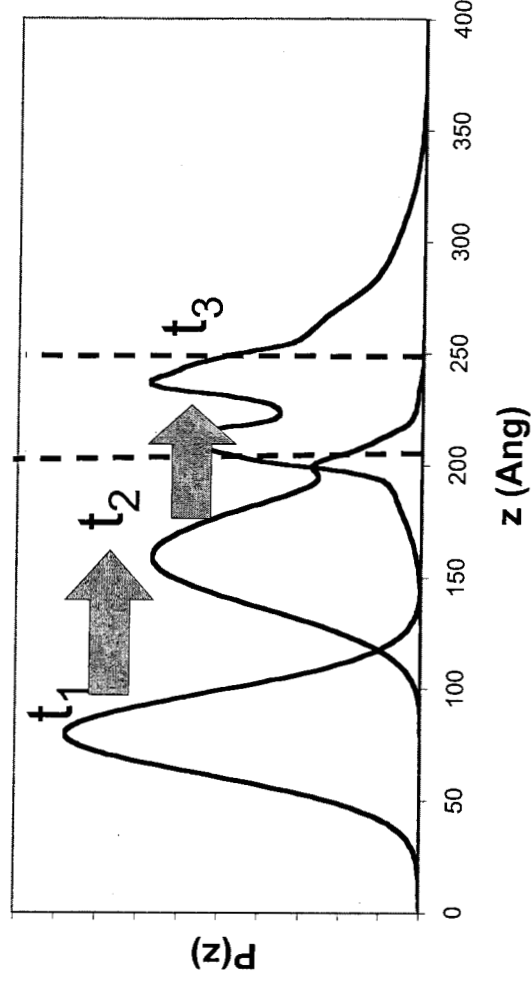
$$v_0 = \frac{D_0 F}{k_B T}$$



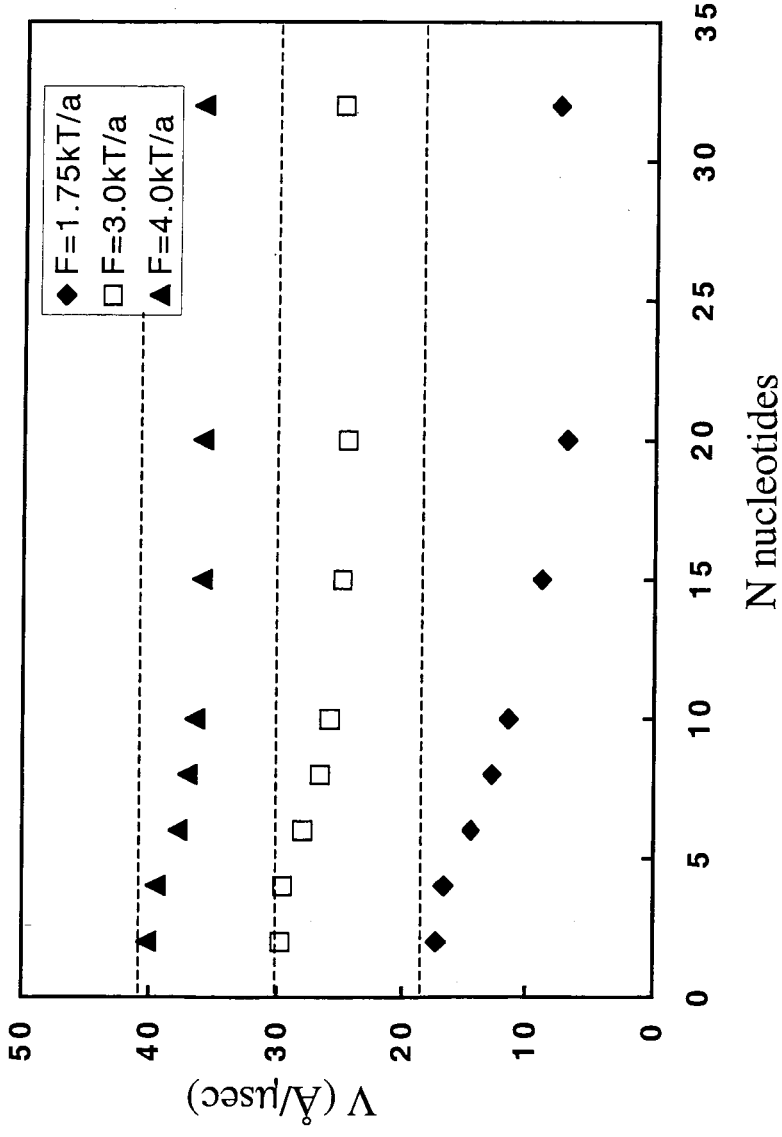
Strong pore interaction

$$\frac{\partial P}{\partial t} = D_0 \frac{\partial}{\partial z} \left[\frac{\partial P}{\partial z} + \frac{U'(z) - F}{k_B T} P \right]$$

$$v < v_0$$



Translocation velocity as a function of polymer length

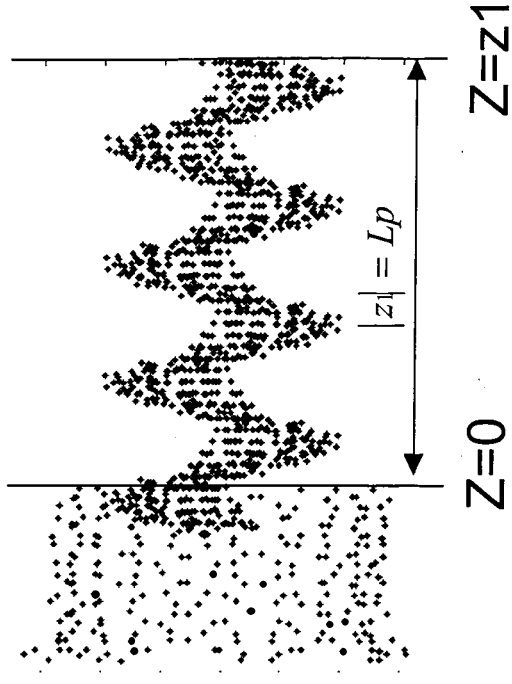


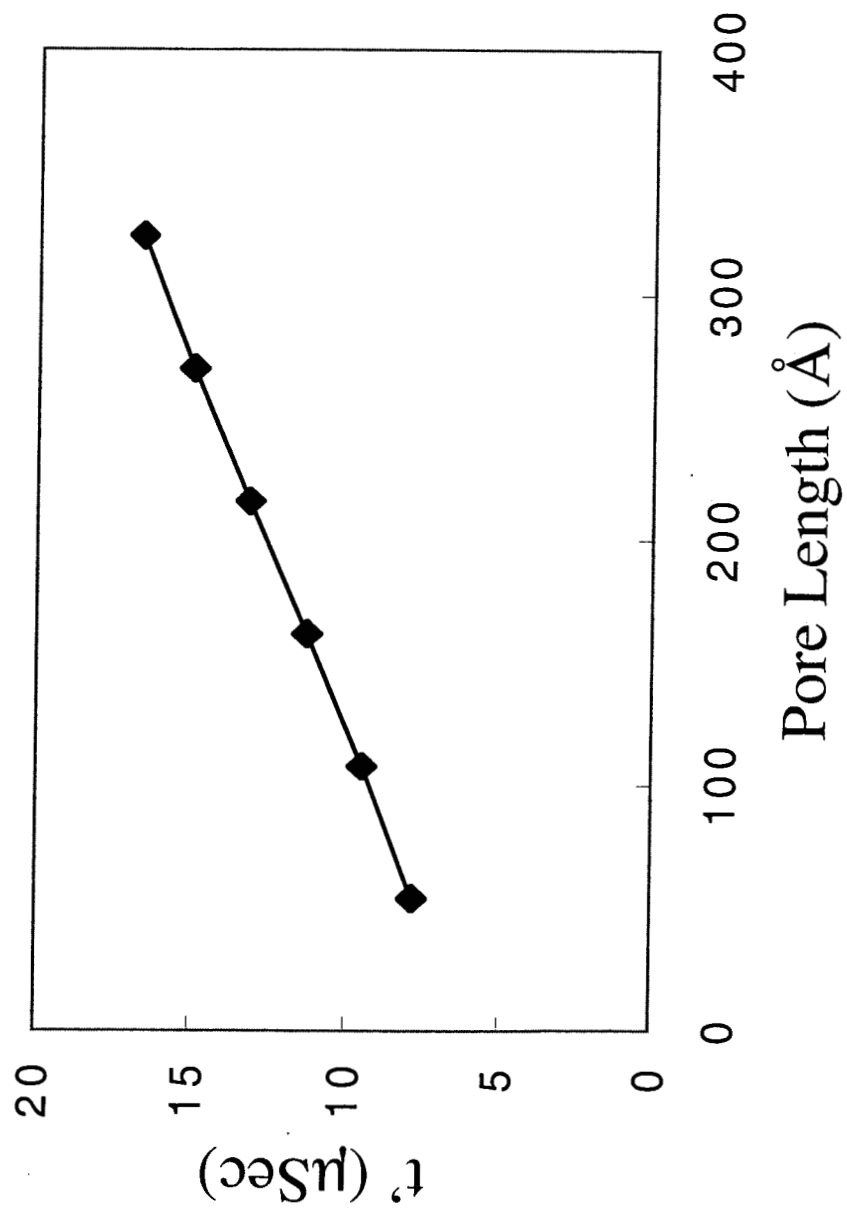
- Translocation velocity v is shown as a function of polymer length N for different driving forces F .
- D_0 is the bare diffusion coefficient for the polymer in water.
- For polymer lengths $N > 20$ the translocation velocity approaches a saturation value v_{sat}

Polymer Translocation time

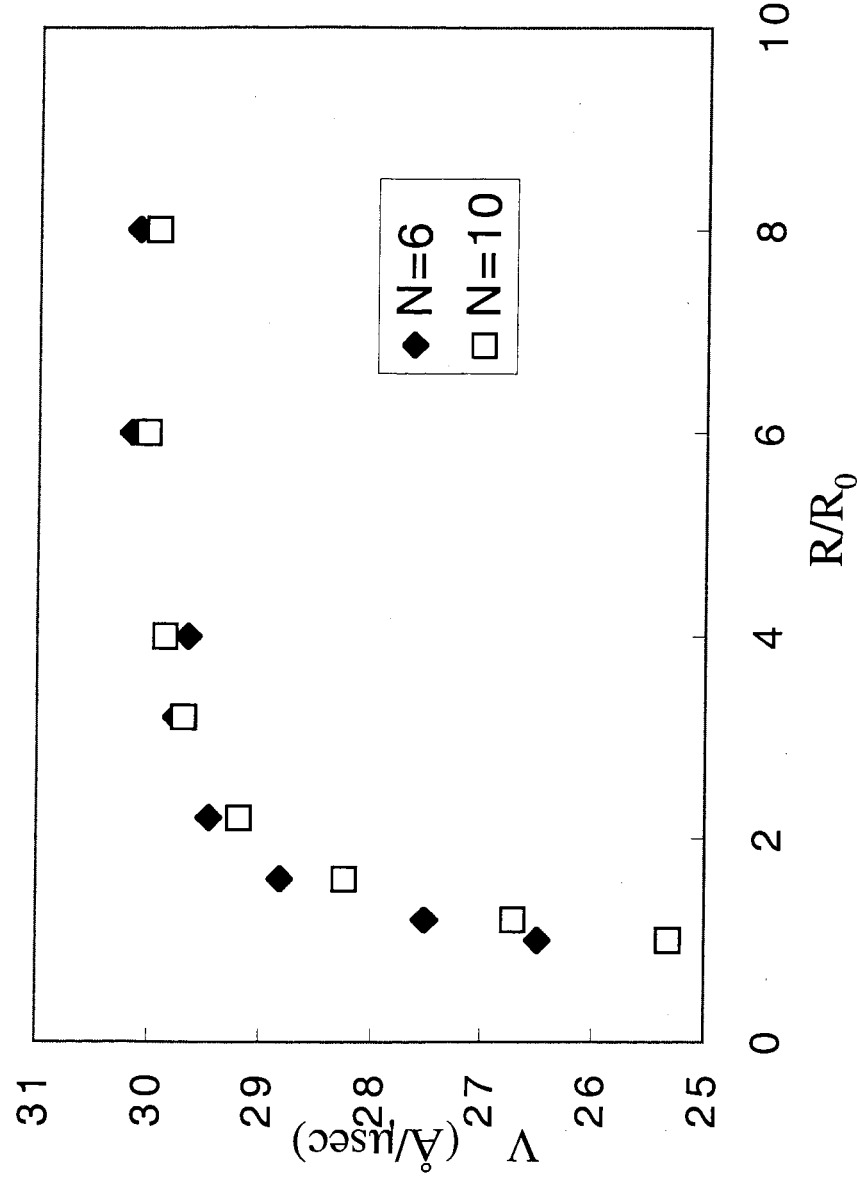
Translocation time t_p

$$\int_{z_1}^{\infty} P(z, t_p) dz = 0.5$$





Polymer velocity as a function of pore radius



- Artificial nanopores are not limited by the same geometry constraints as biological pores. We investigate the effect of uniformly expanding the pore in the (x,y) plane.
- For $R/R_0 > 4$ the polymer velocity approaches the free space value $v \rightarrow v_0 = D_0 F / k_B T$

Conclusions

- A new model for the polymer-pore interaction energy is introduced, based on an atomic-scale description of coulombic polymer-pore interaction.
- The enhanced drift velocity, experimentally observed for short polymers, is successfully accounted for, using this interaction energy model.
- For $R/R_0 > 4$ ($R_0 = 7 \text{ \AA}$) the translocation velocity approaches the free space drift velocity v_0 . This motivates the need to appropriately derivatize artificial nanopores, where $R > R_0$